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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,353	05/09/2005	Jong-Soo Woo	Q87237	4817

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EXAMINER	
PALENIK, JEFFREY T	

ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
09/02/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/534,353	WOO ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Palenik	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *11-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

STATUS OF THE APPLICATION

Receipt is acknowledged of Applicants' Amendments and Remarks, filed 2 July 2010, in the matter of Application N° 10/534,353. Said filings are entered on the record. The Examiner further acknowledges the following:

No claims have been added or amended.

Claims 1 and 10 have been amended changing "recrystallized" to "crystallized". Support for the change is provided. No new matter has been added.

Claims 11-13 remain withdrawn from consideration.

Thus, claims 1-10 continue to represent all claims currently under consideration.

INFORMATION DISCLOSURE STATEMENT

No new Information Disclosure Statements (IDS) have been filed for consideration.

WITHDRAWN OBJECTIONS/REJECTIONS

Rejections under 35 USC 112

Applicants' amendments to claims 1 and 10 render the new matter rejection under 35 USC 112, first paragraph moot. Thus, said rejection has been **withdrawn**.

MAINTAINED REJECTIONS

The following rejections are maintained from the previous Office Correspondence dated 2 April 2010 since the art which was previously cited continues to read on the amended/newly cited limitations.

CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patel et al. (US Pre-Grant Publication 2003/0064097) in combination with Kawamura et al. (US Pre-Grant Publication 2004/0219208).

The instant claims remain drawn to a method for preparing a paclitaxel solid dispersion by a supercritical fluid process as discussed in the Office Action, mailed 21 March 2008. The process comprises dissolving a mixture of paclitaxel and additive in a mixed organic solvent. The solvent is next mixed via spraying with a supercritical fluid; the contact of the two solutions resulting in the formation of paclitaxel/additive particles. Any organic solvent remaining on the particles is washed away using additional supercritical fluid. Lastly, the remaining particles are collected. The instantly amended claim 5 is interpreted by the Examiner as reciting a compositional limitation to claim 1 wherein the hydrophilic polymer (e.g., additive) is present in the solution mixture ranging from 1-75% (w/w) prior to the addition of the supercritical fluid.

Patel et al. teach methods for preparing multiparticulate compositions using processes which comprise applying an encapsulation coat onto a substrate (e.g.., spray coating and nanoencapsulation) as well as collection of the ensuing particles ¶[0223]. Preparation of the encapsulation coating solution is taught as solubilizing or suspending a composition in a mixture comprising an organic solvent and a supercritical fluid, and which can further comprise additives. Paragraph [0039] teaches paclitaxel as one of the most preferred hydrophobic active ingredients used in the encapsulation coating composition. Paragraph [0257] specifically teaches that multiple organic solvents may be combined as the organic solvent of the coating solutions.

Additives are, again, taught as being part of the coating solution composition. Removal of the dispersing medium (e.g.,. the organic solvent of the coating solution) is taught as occurring at the end of the coating process and in the form of drying process (e.g.,. heating, vacuuming, etc.). Recovery of the resulting particles may be accomplished by forming pellets, granules, or spheres, for example ¶[0228].

Patel et al. further teach additives which include hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), and polyvinyl pyrrolidone (PVP) ¶[0166]. PVP, in particular, is taught as both a binder ¶[0166] and a disintegrant ¶[0174]. Where the coating composition is applied to the particles as a delayed release enteric coating, acrylic polymer additives such as methacrylic acid copolymers as well as other polymers of the Eudragit series (e.g.,. E, L, S, RL, and RS) are preferably used ¶¶[0190], [0191] and [0202]. The methods discussed at ¶[0224] employ organic solvents which are further defined at ¶[0257] as mixtures of different solvents such as methanol, ethanol, isopropanol, dichloromethane, and ethyl acetate.

Patel et al. do not expressly teach removal (e..g.,. displacement) of the mixed organic solvent portion of the dispersing medium by washing the coated particles with additional supercritical fluid, but do additionally teach that modifications to the coating process, such as the drying processes, are well known in the art ¶[0226]. Patel et al. also do not expressly teach Applicants' instantly claimed polymer/active weight ratio, percent range of the hydrophilic polymer or the weight ratio of the two organic solvents mixed.

Kawamura et al. teach a process for preparing a sustained-release preparation comprising injectable microcapsules or microspheres ¶¶[0225] and [0226] which comprises an AII

antagonist and an anticancer drug (Abstract; claim 1). Paclitaxel is specifically taught as a plant-derived anticancer agent ¶[0154] which may be employed in the formulation. One such process for preparing said particles or spheres is described in ¶[0259] wherein a compound comprising an AII antagonist and optionally water are added to a solution of additive (e..g.,. biodegradable polymer) in an organic solvent. Paragraph [0263] teaches different ranges of ratios of the organic solvents (i.e. ratio of dichloromethane to ethanol or methanol). Biodegradable polymers such as PVP are taught as emulsifier additives which may be present at preferable concentration ranging from about 0.01-10% by weight ¶¶[0262] and [0265]. Said solution is then finely dispersible by homogenization or by ultrasound over said particles. The organic solvent used is expressly taught as comprising a mixture of different organic-based solvents ¶[0260] as well as an additive ¶[0261] and/or an emulsifier ¶[0265]. Paragraph [0276] teaches methods for removing water and organic solvents from the coated particles which include evaporation and/or vacuuming. A more specific method for removal of water and organic solvent is expressly taught as being performed using a supercritical fluid in a high pressure gas state ¶[0283]. Collection of the resulting microcapsule particles by centrifugation or filtration is taught in ¶[0277].

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a nano-scale paclitaxel solid dispersion (e.g., suspension) by contacting a paclitaxel/additive/mixed alcohol solvent solution with a supercritical fluid, displacing said alcohol solvent with supercritical fluid and recover the resulting particles, as taught and suggested by the combined teachings of Patel et al. and Kawamura et al.

One of ordinary skill in the art would have been motivated to do this because Patel et al.

provides teachings for every aspect of the instantly claimed method except where the organic solvent is removed using supercritical fluid. Patel et al. do teach that at the end of the particle coating process, the residual dispersing medium, which includes the mixed organic solvent, can be further removed to a desirable level utilizing appropriate drying processes such as vacuum evaporation, freeze drying and heating ¶[0224]. The ordinarily skilled artisan, in view of this teaching and ¶[0226], would have been highly motivated to substitute a gas-propelled process for a suction-based process of evaporating organic solvents, such as the solvent removal method taught by ¶[0283] of Kawamura et al., particularly since said removal method explicitly teaches using a supercritical fluid in a high pressure gas-state to remove organic solvents (i.e., mixed ethanol and methanol). Furthermore, while Patel et al. do not expressly teach the claimed order of the addition of components of the instantly claimed method, it would have been *prima facie* obvious to a person of ordinary skill in the art that there is no patentable distinction between Applicants' method and the methods taught in the prior art. The selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results. *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) Selection of any order of mixing ingredients is also held to be *prima facie* obvious. *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (see MPEP 2144.04 (IV)(C.))

Neither of the references explicitly teach polymer/active weight ratio, percent range of the hydrophilic polymer or the weight ratio of the two organic solvents mixed, as claimed by Applicants. The amounts and ratios of specific ingredients in a composition are clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize as is format

of oral dosage (i.e., tablet versus capsule). Optimization of parameters, such as the size of granulated particles, is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amounts and ratios of each ingredient to add in order to best achieve the desired method as cited in the instant claims. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amounts would have been obvious at the time of Applicant's invention.

Given the mixture process steps taught by Patel et al. as well as the modified, supercritical fluid based, organic solvent evaporation step suggested by Patel et al. and taught by Kawamura et al., and since both inventions are directed towards methods for solubilizing insoluble drugs such as paclitaxel in small scale, particulate-based drug delivery compositions, it follows that the combined teachings would have afforded the ordinarily skilled artisan a reasonably high expectation of success for producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the combined references, especially in the absence of evidence to the contrary.

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Patel et al. and Kawamura et al. as set forth above with respect to claim 1 in combination with Nielsen et al. (USPN 5,716,558).

Neither Patel et al. nor Kawamura et al. teach the temperature or pressure application parameters for the supercritical fluid as set forth by Applicants in claim 10.

Nielsen et al. teach methods for spraying liquid compositions by using compressed fluids such as carbon dioxide, to form solid particulates and coating powders which may be produced with narrow particle size distributions (Abstract). Nielsen et al. further teach that compressed carbon dioxide fluid may be sprayed at a temperature of 60°C and a pressure of 1600 pounds/sq. inch (1 bar/14.5 psi; http://onlineconversion.com/pressure.htm) or about 110.3 bar (col. 13, lines 19-26).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to have sprayed a supercritical fluid (e.g., carbon dioxide) using Applicants' instantly claimed physical parameters in view of Nielsen et al's teaching that application of a supercritical fluid to a liquid water-borne polymeric composition comprising a mixed organic solvent produced a dry, collectable powder (Example 9).

RESPONSE TO ARGUMENTS

Applicants' arguments with regard to the rejection of claims 1-9 under 35 USC 103(a) as being unpatentable over the combined teachings of Patel et al. and Kawamura et al., as well as with regard to the rejection of claim 10 under 35 USC 103(a) as being unpatentable over the combined teachings of Patel et al., Kawamura et al. and Nielsen et al. have been fully considered but they are not persuasive.

Applicants initially allege that the combined teachings of Patel et al., Kawamura et al. and Nielsen et al. fail to teach all limitations of the independent claim and "that the feature of the subject invention resides in the unique combination of a drug and a process for forming a solid dispersion" (Remarks, pg. 7, last paragraph). Applicants believe Patel et al. to be simply reciting

a "boilerplate" of active ingredients with little regard for an "improved solubility" in the finished product.

In response, the Examiner initially points out that the Nielsen et al. reference is not relied upon until addressing the limitations of claim 10. Further, the Examiner respectfully disagrees with Applicants' latter remarks and maintains that one of the goals of the Patel et al. invention is to improve the dissolution and/or absorption of a pharmaceutical ingredient ¶[0248]; one of the most preferred of which is paclitaxel ¶[0039].

Applicants next address the Kawamura et al. reference stating simply that it "only teaches that removal of water and organic solvent using supercritical fluid".

Respectfully, the Examiner acknowledges this teaching and points out further that the Kawamura et al. reference, as discussed above, discloses a process employing a multitude of organic solvents and biodegradable polymers in order to prepare the particles later treated with supercritical carbon dioxide. In addition to teaching the use of evaporation/vacuuming to remove the solvent from the particles, Kawamura et al. also specifically discloses that the same removal may be accomplished through the use of supercritical fluid in a high pressure gas state ¶[0283].

Thus given the teachings of Patel et al. to prepare the supercritical mixture and then remove a desirable level of medium using such processes as vacuum evaporation or heating (e.g., evaporating), it stands to reason that the ordinarily skilled artisan would have been similarly motivated to modify Patel et al's method using additional supercritical fluid. Such a motivation stems from the teachings of Kawamura et al. which expressly disclose using supercritical fluid as an alternative means for removing excess solvent from the formed solid particles.

Applicants' remarks concerning the Nielsen et al. reference, directed to claim 10 as discussed above, have been fully considered but are unpersuasive. It is respectfully submitted that it is unclear as to what Applicants' are asserting with regards to the reference. The Examiner relies upon the reference simply to demonstrate that mixing such compressed fluids as supercritical carbon dioxide at the ascribed temperature and pressure is known in the art for forming solid particles, as instantly claimed.

Applicants' remark stated in the penultimate paragraph of page eight of the Remarks, on full consideration, lends support to the position of the Examiner in that 1) the process and parameters are useful in drying (e.g., removing the solvents from) the particles, and 2) motivates the ordinarily skilled artisan to use supercritical fluid in that it is an aesthetically shorter process as and thus one which may be easily repeated (i.e., step 3) application of a fresh batch of SC fluid).

Lastly, Applicants' contrast of Examples 2 and 3 in Patel et al. to the disclosed Examples of the instant invention has been considered but is not persuasive. Applicants readily acknowledge on the record (Remarks, pg. 9, lines 6-9) that the aforementioned Patel et al. Examples respectively depict improving the solubilities of glyburide and progesterone active ingredients. Applicants then appear to use this as a direct comparison to the formulation achieved in the instant invention.

The Examiner respectfully submits that such a comparison is not commensurate in scope with the instant invention as the active ingredients each will have distinct solubilities. Further, as discussed above, the Patel et al. reference alone provides sufficient direction so as to teach and suggest to the artisan of ordinary skill that paclitaxel and an additive may be mixed with organic

solvent(s) in order to form particles upon spray-combination with a supercritical fluid. While the Examiner acknowledges that the Patel et al. reference does not disclose specifically disclose an example(s) incorporating paclitaxel, it is maintained that such combinations are taught and are suggested, particularly since "[a] reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989) [see MPEP §2123(I)]. That being said, each of the different formulations would have been *prima facie* obvious to a person of ordinary skill in the art, absent a clear showing of evidence to the contrary.

For these reasons, Applicants' arguments are found unpersuasive. Said rejection is therefore **maintained**.

All claims under consideration remain rejected; no claims are allowed.

CONCLUSION

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

CORRESPONDENCE

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/
Examiner, Art Unit 1615

/Robert A. Wax/
Supervisory Patent Examiner, Art Unit 1615